AN INTERIM REPORT
ON THE
TREATMENT OF MALARIA.

Abstract of 2,460 Cases. War Office Investigations.

BY

COLONEL SIR RONALD ROSS, K.C.B., F.R.S., A.M.S.,

Consultant in Malaria, War Office.

WITH DISCUSSIONS.

(Paper read at a Meeting of the Society of Tropical Medicine and Hygiene, Friday, February 15th, 1918).

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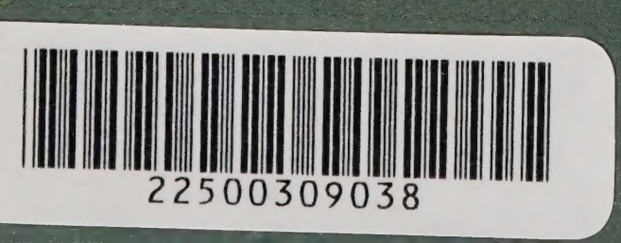

AN INTERIM REPORT ON THE TREATMENT OF MALARIA.

Abstract of 2,460 Cases. War Office Investigations.

BY

Colonel Sir RONALD ROSS, K.C.B., F.R.S., A.M.S.,

Consultant in Malaria, War Office.

[Presented, 24th November, 1917. Postscript, 4th March, 1918.]

(Paper read at a Meeting of the Society of Tropical Medicine and Hygiene, with Discussion, Friday, February 15th, and Adjourned Discussion, Friday, March 15th, 1918.)

I.—Explanatory.

1. Early in 1917 the War Office ordered the concentration of malaria cases in England at a number of special centres, partly that they might receive treatment by specially qualified medical officers, and partly in order to enable a comparison to be made between various lines of treatment which had been previously commended in medical literature, and partly for other investigations on malaria which might be possible. The work was dated by order to commence on the 15th February, 1917, or subsequently, and was carried out first in Aldershot and Liverpool and then in London, Oxford, Epsom, Manchester, Lincoln, Edinburgh, Dublin, and in subsidiary Hospitals; but some delay occurred as regards some of these centres.

2. The present Abstract has been prepared by myself from information furnished by the officers mentioned below, in order to present a general epitome of their work which will be useful to medical officers called upon to treat malaria anywhere. But I have confined myself in it only to the work done at the four hospitals for which I was from the first appointed Consultant in Malaria, namely, the hospitals in Aldershot, London, Oxford and Epsom. The officers concerned with the treatments described below, and with the pathological work and other details, were Lieutenant-Colonel A. D. Milne, C.M.G., E.A.M.S., Lieutenant-Colonel S. P. James, I.M.S., Major R. McCarrison, I.M.S., Major J. B. Stephens, R.A.M.C., Captains H. Meredith Harrison, A. L. Ormerod, J. D. Gimlette, G. B. Bartlett, Dudley Forde, all R.A.M.C.; Captain B. W. Cherrett, E.A.M.S.; Lieutenants R. Dane and W. Murray, R.A.M.C.; Drs. M. C. Beggs and A. C. Delacroix, and Mr. Harold Row, M.B., while special chemical researches have been made by Acting Staff-Serjeant M. Nierenstein. *More detailed reports on the subject will be presented in due course.*

3. The large majority of the cases were infected during 1916 on the Salonika Front, and were cases of benign tertian. Nearly all the cases were diagnosed microscopically in the hospitals mentioned as well as when they were first infected. In a few cases a clinical diagnosis has been accepted at the hospitals though parasites were not found there, but only if a previous microscopical diagnosis had been made in the case. It will therefore be understood that nearly all the cases of fever referred to in this Abstract were relapses; but a very few cases were original infections.

4. It will be seen that the treatments employed in the hospitals concerned are put into four categories:—

Class A, called *Anti-relapse Quinine Prophylaxis*, consist of treatments designed only for preventing relapses as much as possible without attempting absolute cure.

Class B, called *Short Sterilizing Treatments*, were aimed at achieving absolute cure with treatments continued only for a few days, though repetitions of the course may be made.

Class C, called *Long Sterilizing Treatments*, consist of treatments aimed at absolute cure by longer courses, the distinction between Classes B and C being useful though not always very definite.

Class D consist of various mixed treatments, or of treatments with other drugs than quinine.

5. The word "relapse" is necessarily taken here to mean a relapse of fever clinically like malaria, whether asexual parasites are found or not. Where possible, however, the number of relapses in which parasites are found is given; while sometimes sudden increase of asexual parasites without fever has also been noted as relapse—though such cases are comparatively rare. It must be understood that sufficiently detailed examination of the blood could not be made in a certain number of the relapses.

6. When it is stated in the Abstract that a treatment has been given to so many men from such a date to such a date, this implies only that the treatment was practised in the hospital between those dates, not that all the cases were under that treatment during the whole of the period.

7. Relapses occurring in malaria wards during or after a given course of treatment were of course always verified by the special malaria officers. But cases could not be detained indefinitely in hospital for this purpose; and it was therefore necessary to issue notification cards with all cases discharged from the malaria wards, with instructions to report relapses to the said special malaria officers. These instructions have been very largely obeyed; but it is impossible to guarantee that every relapse has been reported. Hence we must infer that the number of relapses recorded in the Abstract is, if anything, *below the true figure.*

8. The number of relapses recorded in the Abstract is, of course, not yet final, partly because more of the cases are likely to relapse in the future, and partly because the further examination of records now being made may disclose the occurrence of relapses which have been hitherto overlooked. I hope therefore to submit corrected figures on a subsequent occasion. By that time it may also be expected that the numbers of cases treated by many of the better methods now reported upon will be considerably increased.

9. Before studying the exact effects of different treatments, it was advisable to obtain some figures as to the frequency of relapses occurring among men who have been taking quinine previously, but for whom this medication has now stopped. Accordingly 193 men who were admitted at Oxford, either for attacks actually in progress or for recent attacks before admission, were watched carefully without any quinine treatment

at all. Of these 193 men, 88 relapsed within 27 days after treatment; 76 were not sufficiently well to allow of the quinine being withheld any longer; and only 29 were considered well enough to be discharged from hospital without treatment, as the exigencies of service demanded. We may thus suppose that during the month only 15 per cent. of the men who remained untreated by quinine escaped either relapses or illness—so that 85 per cent. of such untreated cases remained ill and 45·6 per cent. actually suffered from relapses during the period. These studies were made from the 23rd March, 1917, to the 17th October, 1917. The following table gives the results in detail :—

TABLE.

Number of days until patients got fever	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Number of men who got fever	3	6	8	5	4	7	5	9	8	9	4	6	3	3	1
Numb'r of men giv'n quinine before fev'r commenced ...	1	1	1	3	5	3	8	6	2	7	7	4	8	5	2
Number of men discharged without fever or quinine ...	—	—	—	—	—	—	1	1	2	—	1	1	—	1	2

Number of days until patients got fever	18	19	20	21	22	23	24	25	26	27	28	30	34	38	Tot.
Number of men who got fever	—	2	—	1	3	—	—	—	—	1	—	—	—	—	88
Numb'r of men giv'n quinine before fev'r commenced ...	—	3	1	1	1	—	—	—	3	2	1	—	1	—	76
Number of men discharged without fever or quinine ...	2	5	1	3	1	2	1	—	2	—	1	1	—	1	29

II.—ABSTRACT.

A.—*Anti-relapse Quinine Prophylaxis.*

1. *Epsom.*—Quinine sulphate, 5 grains orally in solution at 11 a.m. once a day.

Given to 61 cases from 7th May, 1917, to 21st June, 1917.

Of these 21 relapsed (33 per cent.) while taking the quinine; parasites found in 6 relapses, not found in 6 relapses, not looked for in 7 relapses, and 2 cases shewed parasitic relapses without fever.

Average duration of treatment, 28 days.

2. *Epsom.*—Quinine sulphate, 10 grains orally in solution once a day at 11 a.m.

Given to 315 cases from 17th May, 1917, to 21st September, 1917.

Of these, 58 relapsed (15·2 per cent.) whilst taking the quinine; parasites found in 9, not found in 33, not looked for in 13, and 3 cases shewed parasitic relapses without fever. Of the 58 relapses, 38 cases had fever for one day only, and only 20 had fever for more than one day, or had fever combined with presence of parasites in blood, and these 20 cases alone (6·4 per cent.) were considered by the Medical Officer to be true relapses.

Average duration of treatment, 33 days.

Treatment well borne. Patients improved rapidly.

3. *Epsom.*—Quinine sulphate, 15 grains orally in solution once a day at 11 a.m.

Given to 119 cases from the 1st July, 1917, to 21st September, 1917.

Of these, 20 relapsed (17 per cent.) while taking the quinine; parasites found in 3, not found in 14, and not looked for in 3. Out of the 20 cases which relapsed, only 4 (3·4 per cent.) had fever for more than one day, or had one day's fever with parasites in blood.

Average duration of treatment, 31 days.

Treatment well borne, but not so well as previous treatment.

4. *Oxford.*—Quinine sulphate, 10 grains orally in solution in hydrobromic acid once a day.

Given to 151 men from 29th June, 1917, to 30th September, 1917.

Of these, 12 relapsed (8 per cent.) while taking the quinine; parasites found in 8, not found in 3, and not looked for in 1. In the cases which relapsed, the periods of treatment to dates of relapse varied from 3 to 32 days, average 12·5 days.

Average duration of treatment, 30 days.

Treatment well borne. Patients improved rapidly.

5. *Oxford.*—Quinine sulphate, 20 grains orally in solution in hydrobromic acid every Saturday, and the same also on every Sunday, in 10-grain doses morning and evening. Patients allowed out, and go for route marches.

Given to 262 cases from 9th June, 1917, to 30th September, 1917.

Of these, 22 relapsed (8·35 per cent.) while taking the quinine; parasites

were found in 1 out of 2 cases only which were searched for them. In the cases which relapsed, the periods of treatment to dates of relapse varied from 4 to 49 days, the average being 20·5 days.

Average duration of treatment, 48 days.

Treatment well borne. Patients improved rapidly.

6. *Oxford.*—Quinine is given when a relapse is due, or when the patient feels that an attack is impending, or occasionally if he has a foot-hill temperature. The dose and salt used vary, and the patients go for route march in the morning and are allowed out of doors all the evening.

Given to 132 cases from 8th May, 1917, to 31st August, 1917. Of these, 39 relapsed (30 per cent.) while taking the treatment; parasites found in 16, not found in 21, while two cases shewed parasitic relapses without fever. In the cases which relapsed, the periods of treatment to dates of relapse varied from 4 to 54 days, average 20 days.

Average duration of treatment, 37 days.

Treatment well borne.

Remarks.—Many of the relapses occurred immediately after the treatment was commenced and before it could have affected the patient materially. On the other hand, some of the patients had been previously treated for fever on admission by considerable doses of quinine until the temperature fell to normal, and the anti-relapse quinine prophylaxis was commenced only after such previous large-dose treatment.

In all these lines of treatment the patients did very well indeed, put on flesh, and were easily able to take exercise; and when the relapses occurred they were generally very slight.

B.—*Attempted Short Sterilizing Treatments.*

1. *Oxford.*—Quinine sulphate in solution in hydrobromic acid, orally, in doses of 40, 60, and 80 grains on 3 successive days, or in doses of 20, 40, 60, 80 grains on 4 successive days; these daily quantities of quinine divided into 5 doses, each dose being administered before each meal and at bed-time. Quinine treatment then stopped altogether.

Given to 154 cases from 3rd May, 1917, to 30th June, 1917.

Of these, 30 relapsed (19·5 per cent.) up to 30th June, 1917; parasites were found in 18 cases, and apparently not found or looked for in the rest.

The relapses were found in an average of 15 days after the end of the treatment (extremes 9-28 days).

The treatment was immediately effective and well borne, though some complaints were made regarding the last dose.

2. *London.*—Quinine sulphate, 60 grains orally in one dose daily for 2 days ; or single doses of the alkaloid, 60 grains orally ; or smaller doses of the alkaloid orally for 3 days.

Given to 7 cases from 1st April, 1917, to the 31st May, 1917.

Of these, 4 relapsed (57 per cent.) up to 10th June, 1917.

The relapses occurred in an average of 5 days (extremes 1 to 10 days).

The treatment was not well borne as a rule. Albuminuria occurred in some cases, pronounced gastric disturbance in others, while in one case cardiac failure occurred. The temperature fell rapidly, but parasites persisted for 4-5 days.

3. *London.*—Hydrochloride of quinine in subcutaneous injection, 22½ grains in 3 c.c. of sterile fluid (Parke, Davis and Company's ampules used), daily in a single dose for 7 days.

Given to 9 cases from 1st April, 1917, to 31st May, 1917.

Of these, 6 relapsed (67 per cent.) up to 14th June, 1917.

The relapses occurred in an average of 15·2 days (extremes 2 to 30 days). The 6 relapsed with fever and parasites. Records of three other cases after discharge have not been received.

Temperature fell to normal in 48 hours, except in one case which remained slightly above normal for 5 days. Parasites disappeared as a rule in 4 days but in one case were present till the sixth day, and in another *P. falciparum* case parasites were found till the eleventh day from the commencement of the treatment.

The treatment is disliked by the patients. It may cause sloughing under most aseptic precautions, also subacute cellulitis, and in one case paralysis of the musculo-spiral nerve.

Medical Officer considers the treatment ineffective as a curative procedure, and dangerous when such concentration of the drug is introduced under the skin.

4. *London.*—Quinine hydrochloride, 22½ grains in 3 c.c. of sterile fluid by intramuscular injection in a single dose daily for seven days.

Given to 5 cases from the 1st April, 1917, to 31st May, 1917.

Of these, 3 relapsed (60 per cent.) up to the 14th June, 1917. The 3 cases relapsed with fever and parasites. The relapses occurred in an average of 14 days (extremes 0-3 days).

Temperature became normal in 48 hours. Parasites disappeared from the blood on the fourth day in all cases.

The patients did not like the treatment. It is not so painful as the subcutaneous method. No ill effects beyond pain and stiffness.

5. *London.*—Quinine hydrochloride, 22½ grains orally, in a single dose daily for 7 days.

Given to 5 cases from 1st April, 1917, to 31st May, 1917.

Of these, 4 relapsed (80 per cent.) up to the 14th June, 1917.

The relapses occurred in an average of 16 days (extremes 14-20 days). Fever and parasites were present in all relapses.

The treatment was well borne.

Medical Officer considers the treatment good for controlling the attack, but that it has no effect in preventing relapses.

6. *London.*—(Ochsner's Treatment.) Quinine sulphate or hydrochloride, 2 grains in solution orally every two hours night and day for 60 hours, followed after each dose by half a pint of water. At the end of 60 hours, arsenious acid 5 times in $\frac{1}{5}$-grain doses for 5 days with hot water with each dose. Then the 2-grain treatment as above for another 60 hours. Ol. Ricini the night before treatment is commenced. Diet throughout treatment is beef tea only.

Given to 35 cases from the 1st April, 1917, to 15th June, 1917.

Of these, 19 relapsed (54 per cent.) up to 15th June, 1917.

The relapses occurred in an average of 21 days (extremes 5-53 days). Fever and parasites were present in all relapses.

Temperature and parasites usually disappeared within three days; but the parasites may reappear in 4 or 5 days during the arsenic period. The second quinine treatment causes them to disappear again.

The treatment was not well borne. During treatment patients became weak from starvation. They passed enormous quantities of urine.

Medical Officer considers the method unpractical on account of difficulty of getting cases to stick to it. Those who continued either did not relapse or took longest to relapse.

7. *London.*—Quinine sulphate or hydrochloride, 5 grains orally every 2 hours night and day for 48 hours, until 120 grains quinine are taken.

Then arsenious acid 1-50th grain 5 times daily for 5 days. Then 5 grains quinine orally for every two hours for 48 hours as above. Slop diet and plenty of hot water.

Given to 25 cases from the 1st April, 1917, to 15th June, 1917.

Of these, 11 relapsed (44 per cent.), 8 with fever and parasites and 3 with fever alone up to the 15th June, 1917.

The relapses occurred in an average of 14 days (extremes 3-30 days).

The temperature fell rapidly and the parasites generally disappeared from the blood within three days. Parasites sometimes reappear during the intervals between the first and second courses of quinine. The second course of quinine causes their disappearance.

Treatment well borne. Objection : Being awakened at night.

8. *London.*—Quinine hydrochloride, 20 grains orally, 3 times a day for 2 days ; then iron and arsenic for 5 days ; then quinine hydrochloride again as above for another 2 days. Hospital diet.

Given to 34 cases from 1st April, 1917, to 15th June, 1917.

Of these 6 relapsed (18 per cent.) up to 15th June, 1917 ; 4 relapsing with fever and parasites, 1 with fever alone, and 1 with parasites alone.

The relapses occurred in an average of 7 days (extremes 5 to 10 days).

Temperature falls to normal within 3 days. Asexual parasites disappear within 3 days. Sexual parasites tend to persist longer.

Treatment is well borne as a rule. In some cases evidence of high dosage occurred, such as cardiac distress, etc.

9. *London.*—Quinine hydrochloride by intravenous injection, 15 grains daily in from 1 to 6 injections.

Given to 6 cases from 1st April, 1917, to 15th June, 1917.

Of these, 2 relapsed (33 per cent.) up to the 15th June, 1917 ; 2 with fever and parasites.

The relapses occurred in an average of 26 days (extremes 12-30 days).

Temperature falls and parasites disappear from blood rapidly.

Treatment is well borne.

Medical Officer considers that the attack is controlled but that relapses are not prevented.

10. *Aldershot.*—Quinine bihydrochloride by intramuscular injections in 4 doses of 10 grains each on the first day ; 4 doses of 15 grains each on the second day, and 4 doses of 15 grains each plus 2 doses of 10 grains

each on the third day. Patient kept in bed 7 days. No further medicinal treatment.

Given to 21 cases from the 10th April to 7th September, 1917.

Of these, 13 relapsed (62 per cent.) up to 31st December, 1917. Parasites present in all.

The relapses occurred in an average of 45 days (extremes 16-113 days).

Treatment was well borne and quickly effective.

11. *Aldershot.*—Quinine hydrochloride orally, 40 grains in solution with lemonade in 1 dose on first day; 60 grains similarly on second day; 80 grains on third day; all with 2 ounces of port wine half an hour after the dose; patient kept in bed for 7 days.

Given to 4 cases from the 22nd to 29th April, 1917.

Of these, 2 relapsed (50 per cent.) up to the 31st December, 1917, parasites being found in both relapses.

One case relapsed on the 16th and the other on the 31st day.

Treatment reduced fever and parasites within 42 hours but was badly borne, vomiting occurring after 60-grain doses.

12. *Aldershot.*—Quinine bihydrochloride by intramuscular injection in 2 doses of 10 grains each daily for 7 days; patients being kept in bed. No further quinine treatment.

Given to 19 cases from 2nd April, 1917, to 1st May, 1917.

Of these, 8 relapsed (42 per cent.) up to 31st December, 1917. Parasites were found in all relapses.

The relapses occurred in an average of 29 days (extremes 11 to 73 days).

Treatment was well borne and quickly effective.

13. *Epsom.*—Quinine bihydrochloride injected intravenously in doses of 6 grains or of 15 grains once daily, on from 2 to 10 consecutive days. No further treatment except a little oral treatment in two cases.

Given to 10 cases from 10th May, 1917, to 25th June, 1917, all these cases being benign tertian.

Of these, 7 relapsed (70 per cent.) up to 25th June, 1917, parasites in 6, fever only in one. Three of the relapsing cases had received injections on ten consecutive days.

The relapses occurred in an average of 6·4 days (extremes 0 to 13 days).

Treatment quickly but not permanently effective. See also, for details,

the article by Lieutenant-Colonel James, I.M.S., in *Journal R.A.M.C.*, September, 1917

C.—*Attempted Long Sterilizing Treatments.*

1. *Oxford.*—Quinine sulphate in solution in hydrobromic acid, 20 grains, orally, daily for 3 days; then 25 grains of the same salt daily for another 3 days; then 30 grains daily for another 3 days; then 35 grains daily for another 3 days; then 40 grains daily for 2 days; that is during a total of 14 days. These daily quantities of quinine were divided into 5 doses, 1 dose before each meal and 1 at bedtime. Quinine treatment was then stopped altogether.

Given to 99 cases from 22nd March, 1917, to 9th May, 1917.

Of these, 27 relapsed (27 per cent.) up to 19th June, 1917. Parasites were found in all relapses.

Relapses occurred in an average of 17 days after the end of the treatment (extremes 9 to 35 days).

The treatment was well borne and immediately effective.

2. *Oxford.*—Quinine sulphate precisely as above except that the 40 grains were given daily for 9 days, so that the whole treatment extended over 21 days.

Given to 50 cases from 22nd March, 1917, to 12th May, 1917.

Of these, 12 relapsed (24 per cent.) up to 19th June, 1917. Parasites were found in all the relapses.

The relapses occurred in an average of 16 days after the end of the treatment (extremes 8 days to 25 days).

The effects as in 1.

3. *Oxford.*—Quinine sulphate as in 1 except that the 40 grains daily were continued for 1, 2, 3 days more, so that the whole treatment lasted from 15 to 18 days

Given to 45 cases from 27th March to 20th May, 1917.

Of these, 10 relapsed (22 per cent.) up to 11th June, 1917. Parasites were found in (?) cases.

The relapses occurred in an average of 21 days (extremes 12 to 38 days).

The effects as 1 and 2.

4. *Oxford.*—Quinine sulphate precisely as in 1 except that the 40 grains were given daily for 7 or 8 days at the end of the course so that the whole treatment lasted 19 or 20 days.

Given to 35 cases from 23rd March, 1917, to 29th April, 1917.

Of these, 8 relapsed (23 per cent.) up to 19th June, 1917. Parasites were not looked for in the relapses.

The relapses occurred in an average of 16 days (extremes 8-22 days).

The effects as in 1, 2 and 3.

5. *Oxford.*—Quinine sulphate as in previous treatments, the dosage being increased from 20 grains daily to 80 grains daily during 22 days, or from 20 grains daily to 60 grains daily during 16 days.

Given to 59 cases from 13th April, 1917, to 12th May, 1917.

Of these, 8 relapsed (13·6 per cent.) up to 19th June, 1917. Parasites found in two, not found in one, not looked for in five.

The relapses occurred in an average of 13 days after the end of the treatment (extremes 10-16 days).

The effects as before, but complaints were made regarding the large doses at the end of the treatment.

6. *Epsom.*—Quinine sulphate in solution orally in doses varying from 10 to 12 grains 4 times a day every day for 3 weeks.

Given to 189 cases from 7th April to 12th June, 1917.

Of these, 114 relapsed (61 per cent.) up to 12th June, 1917. Parasites were found in 73 relapses, fever only was present in 41 of the relapses.

The relapses occurred in an average of 15 days after the end of the treatment (extremes 2-30 days).

The treatment was generally immediately effective in reducing fever and parasites, and was well borne in the majority of cases.

7. *London.*—Quinine sulphate in solution orally, 10 grains three times a day for 21 days.

Given to 63 cases from 1st April, 1917, to 15th June, 1917.

Of these, 40 relapsed (63·5 per cent.) up to 15th June, 1917. Parasites found in 28, not found in two, not looked for in 9, and without fever in 1.

The relapses occurred in an average of 17 days (extremes 1-34 days).

Temperature fell to normal in 3 days. Asexual parasites disappeared in 4 to 5 days. Sexual parasites persisted for 14 days or more.

The treatment was well borne as a rule, though a number of cases shewed one or more of the following symptoms: Headache, giddiness. deafness, buzzing in the ears, restlessness, conjunctivitis, bladder irrita-

tion, amblyopia, blackwater fever, vomiting and gastric irritation, mental confusion, and a proportion shewed signs of cardiac distress. The method does not seem to be curative.

8. *London.*—Quinine sulphate, 20 grains or less in solution, orally, in a single dose daily 4 hours before expected rigor, the dosage being gradually reduced to 10 grains in a single dose daily 4 hours before the expected rigor.

Given to 40 cases from 1st April, 1917, to 15th June, 1917.

Of these none relapsed up to 15th June, 1917, the patients being given quinine during the whole period.

The temperature drops to normal within 3 days. Asexual parasites disappear from the blood within 4 days.

The treatment was well borne.

The Medical Officer considers this the best of all treatments; but the subsequent history of the patients has not yet been determined, and it is probable that many relapsed after the treatment ceased.

9. *Aldershot.*—Quinine bihydrochloride by intramuscular injections in 10-grain doses in each deltoid muscle at the same time, and 4 other injections of 10 grains each at intervals of 4 hours, totalling 60 grains for the first day. After this, 10 grains, orally, every 4 hours, totalling 40 grains for from 10 to 14 days; after this, 5 grains, orally, 4 times a day for another 3 weeks. The patient is allowed up on the third day with full diet with extras.

Given to 23 cases from 5th July, 1916, to 26th March, 1917.

Of these, 12 relapsed (55 per cent.) up to 31st December, 1917. Only relapses in which parasites were found are counted.

The relapses occurred in an average of 21 days after the end of the treatment (extremes 0 to 45 days).

Temperature fell in from 12 to 24 hours. Asexual parasites disappeared within 48 hours.

The treatment was always well borne. The oral quinine was combined with strychnine, arsenic and iron.

10. *Aldershot.*—As above, except that the injections on the first day amounted only to 40 grains.

Given to 50 cases from 20th September, 1916, to 26th March, 1917.

Of these, 20 relapsed (40 per cent.) up to 31st September, 1917.

The relapses occurred in an average of 27 days after the end of the treatment (extremes 10 to 54 days).

Treatment was well borne. Fever reduced within 24 hours and asexual parasites disappeared within 48 hours.

11. *Aldershot.*—Quinine bihydrochloride in intramuscular injections in two doses of 10 grains each daily for 3 days; then quinine sulphate or hydrochloride, 10 grains, orally, 4 times a day for 10 to 14 days; then the same salt, 5 grains, orally, 4 times daily for 3 weeks more, with strychnine, iron and arsenic.

Given to 104 cases from 14th February, 1917, to 19th May, 1917.

Of these, 61 relapsed (59 per cent.) up to 31st December, 1917. Parasites in all relapses.

The relapses occurred in an average of 25 days after the end of the treatment (extremes 0 to 102 days).

The treatment was well borne and quickly effective. Doses given as far as possible when rigor was due.

12. *Aldershot.*—Quinine bihydrochloride in intramuscular injections of 15 grains each in each deltoid simultaneously, 30 grains daily for three days, followed by quinine hydrochloride, 40 grains daily, orally, continued with strychnine, iron and arsenic for three weeks more.

Given to 10 cases from 29th April, 1917, to 30th June, 1917.

Of these, 3 relapsed (30 per cent) up to 30th September, 1917.

The relapses occurred in an average of 16 days (extremes 6 to 21 days).

The treatment was well borne and quickly effective.

13. *Aldershot.*—Quinine bihydrochloride by intramuscular injections of 15 grains in each deltoid simultaneously, that is 30 grains daily for 7 days. The patient kept in bed for seven days. No further quinine treatment.

Given to one case which relapsed in ten days.

14. *Aldershot.*—Quinine hydrochloride, 10 grains, orally, with strychnine, arsenic and iron, 4 times daily for 14 days, followed by quinine hydrochloride, orally, 5 grains, 4 times daily for 21 days.

Given to 6 cases from 7th April to the end of May, 1917.

Of these, 2 relapsed (33 per cent.) up to 30th September, 1917. Parasites found in both.

Treatment well borne. Temperature and asexual parasites disappeared within 72 hours.

15. *Aldershot.*—Quinine bihydrochloride by intramuscular injections, 15 grains in 4 doses plus 40 grains orally, totalling 100 grains daily, for 3 days, the patient being kept in bed for 7 days. After the 3 days, quinine hydrochloride, 15 grains, orally, 4 times daily for 10 days more and then 20 grains of the same salt daily for 14 days more, combined with strychnine, arsenic and iron. Port wine daily, 2 ounces after injections, with generous diet.

Given to 109 cases from 25th April, 1917, to 14th August, 1917.

Of these, 25 relapsed (23 per cent.), up to 31st December, 1917.

Relapses occurred in an average of 40 days (extremes 10 to 116 days).

Treatment quickly effective, well borne and not much vomiting. See remarks below.

16. *Aldershot.*—Quinine hydrochloride, orally, 15 grains in solution 4 times (totalling 60 grains) daily for 14 days (7 days in bed) followed by 5 grains of same salt orally 4 times daily for 14 days more, all with strychnine, arsenic and iron.

Given to 95 cases from 25th April, 1917, to 30th September, 1917.

Of these, 19 relapsed (20 per cent.) up to 30th September, 1917.

Relapses occurred in an average of 28 days (extremes 9 to 58 days).

Vomiting more pronounced than in previous cases.

See remarks below.

17. *Aldershot.*—Quinine bihydrochloride by intramuscular injection, 15 grains simultaneously in each deltoid with 10 grains, orally, of hydrochloride thrice daily, totalling 60 grains daily, for 12 days, patient remaining in bed for 12 days.

Given to 49 cases from 10th July, 1917, to 22nd October, 1917.

Of these, 5 relapsed (10 per cent.) up to 31st December, 1917.

Relapses occurred in an average of 34 days (extremes 16 to 72 days).

Treatment quickly effective and well borne.

Medical Officer thinks that the 12 days' rest in bed is of great value, and would advocate three weeks of such rest. He thinks that this is the best form of treatment yet used by him.

See remarks below.

18. *London.*—Quinine hydrochloride, 10 grains, 3 times daily, orally, for 21 days, followed by quinine hydrochloride, 60 grains, orally, every week for two months, in variously divided doses.

Given to 13 cases from 1st September, 1917, to 31st October, 1917.

Of these, 4 relapsed (31 per cent.) with parasites up to 6th November, 1917.

Temperature and parasites disappeared rapidly.

The treatment was well borne. In some cases the full course has not yet been completed.

19. *London.*—Quinine bihydrochloride, 15 grains, by intramuscular injections in the gluteal region, in 3 c.c. of normal saline daily for 7 days followed by quinine sulphate, 60 grains weekly, orally, for two months in variously divided doses.

Given to 4 cases from 1st September, 1917, to 31st October, 1917.

Of these, 1 case relapsed (25 per cent.) up to 6th November, 1917.

Treatment was well borne.

20. *London.*—Quinine sulphate 10 grains, orally, 3 times a day for 21 days, followed by quinine sulphate, 60 grains, orally, for two months, in variously divided doses.

Given to 11 cases from 1st September, 1917, to 31st October, 1917.

Of these, 1 relapsed (9 per cent.) up to 6th November, 1917. Case relapsed before end of treatment.

Treatment was well borne. The full course was not completed by any of the cases of this series up to date of report (6th November, 1917).

21. *London.*—Quinine sulphate, 10 grains 3 times a day, orally, for 7 days, followed by quinine sulphate, 60 grains weekly, orally, for two months, in variously divided doses.

Given to 1 case from 1st September, 1917, to 31st October, 1917.

This case relapsed at once.

Treatment was well borne. Attack was cut short.

22. *London.*—Quinine hydrobromide, 10 grains, orally, 3 times a day for 21 days, followed by quinine sulphate, 60 grains, orally, weekly for two months, in variously divided doses.

Given to 11 cases from 1st September, 1917, to 31st October, 1917.

Of these, 7 relapsed (64 per cent.), 5 with parasites only and 2 with fever and parasites.

Treatment was well borne and effective. The relapses all occurred before the end of the full course of treatment,

Remarks.—On the 16th and 17th November, 1917, I inspected 97 of the men who had been through the Aldershot courses C 15, 16 and 17, and found that unfortunately many of them had been given daily doses of quinine (generally only 5 grains) by the medical officers of their units after they had been discharged from the special malaria wards. The low proportion of relapses in these three treatments (8 to 20 per cent.) may be partly due to this continued medication; but as none of the 79 men had returned to hospital, and only six of them looked at all unwell, I gathered that this continued medication had been unnecessary, and that most of the men had been really cured. Further study of these cases is in progress. See Postscript.

D.—*Mixed Treatments.*

1. *London.*—Tartar emetic, $\frac{1}{3}$ grain first day, $\frac{2}{3}$ grain third day, 1 grain fifth day, by intravenous injection in 3 c.c. of normal saline followed by quinine hydrochloride, grains 10, orally 3 times a day for 21 days.

Given to 5 cases from 1st April, 1917, to 31st October, 1917.

Of these, 2 relapsed (40 per cent.) up to 6th November, 1917. Parasites persisted unaffected.

Treatment was well borne. Only given in cases shewing crescents. One medical officer reports that the injections had a tonic effect.

2. *London.*—Acid arsenoids, 1/50th grains in pill, 3 times a day orally for 21 days.

Given to 6 cases from 1st September, 1917, to 31st October, 1917.

Of these, 4 relapsed (66 per cent.), 2 with fever and asexual parasites and 2 with fever only.

Treatment was well borne.

3. *London.*—Sodium quinine sulphonate, 10 grains, 3 times a day orally for 9 days.

Given to 2 cases from 1st September, 1917, to 31st, October, 1917.

The 2 cases relapsed with fever and parasites.

The treatment was well borne but appears to be of no value.

4. *London.*—Ethyl quitenine hydrochloride, 10 grains, 3 times a day orally for 21 days.

Given to 3 cases from 1st September, 1917, to 31st October, 1917.

Of these, all relapsed up to 6th November, 1917. One with fever and parasites and 2 with fever only.

The treatment was well borne. The drug does not seem to be efficacious.

5. *London.*—Collosol quinine by intravenous injection 10 c.c. in one dose.

Given to 2 cases from 21st to 22nd September, 1917.

Of these, 2 relapsed with fever and parasites, up to 6th November, 1917.

Treatment was well borne. Given only in crescent cases. No effect on fever or parasites.

6. *London.*—Collosol quinine, half an ounce, 3 times a day orally for 10 days.

Given to one case from the 1st April, 1917.

No effect whatever on the parasites.

Treatment was well borne.

III.—Synopsis.

A.—*Anti-Relapse Quinine Prophylaxis.*

Treatments.	1	2	3	4	5	6	Totals.
Number of cases ...	61	315	119	151	262	132	1,040
Number of relapses ...	21	58	20	12	22	39	172
Percentage	33·0	15·2	17·0	8·0	8·4	30·0	16·5

B.—*Short Sterilizing Treatments.*

Treatments.	1	2	3	4	5	6	7
Number of cases ...	154	7	9	5	5	35	25
Number of relapses ...	30	4	6	3	4	19	11
Percentage	19·5	57·0	67·0	60·0	80·0	54·0	44·0

B.—*Short Sterilizing Treatments*—cont.

Treatments.	8	9	10	11	12	13	Totals.
Number of cases ...	34	6	21	4	19	10	334
Number of relapses ...	6	2	13	2	8	7	115
Percentage	18·0	33·0	62·0	50·0	42·0	70·0	34·0

C.—*Long Sterilizing Treatments.*

Treatments.	1	2	3	4	5	6	7	8
Number of cases ...	99	50	45	35	59	189	63	40
Number of relapses ...	27	12	10	8	8	114	40	0.0
Percentage	27·0	24·0	22·0	23·0	13·6	61·0	63·5	0·0

Treatments.	9	10	11	12	13	14	15	16
Number of cases ...	23	50	104	10	1	6	109	95
Number of relapses ...	12	20	61	3	1	2	25	19
Percentage	55·0	40·0	59·0	30·0	100·0	33·0	23·0	20·0

Treatments.	17	18	19	20	21	22	Totals.
Number of cases	49	13	4	11	1	11	1,067
Number of relapses	5	4	1	1	1	7	381
Percentage	10·0	31·0	25·0	9·0	100·0	64·0	35·7

D.—*Mixed Treatments.*

Treatments.	1	2	3	4	5	6	Totals.
Number of cases	5	6	2	3	2	1	19
Number of relapses	2	4	2	3	2	1	14
Percentage	40·0	66·0	100·0	100·0	100·0	100·0	74·0

Total cases	2,460
Total relapses	682
Percentage	27·7

IV.—Chemical Researches.

Staff-Serjeant M. Nierenstein is preparing a full and lengthy report of his numerous investigations on quinine. The summary of his interim report (from 13th April to 31st December) is as follows:—

" So far as it is possible to summarise provisionally the above results, it seems more or less apparent that there is a tendency for the excretion of the quinine passed to reach a concentration of 7 to 11 grains per litre of urine. This appears to be the case for all salts experimented with (except the lactate), and the fact does not appear to be altered by the different methods of administration. Thus these results flatly contradict all statements to the effect that quinine given intramuscularly or intravenously is more or less readily excreted than quinine given orally. Moreover, no one quinine salt appears to be more readily eliminated in the form of its base than another salt. These results have been obtained from 1,366 analyses made on 624 different specimens; and have since been confirmed in quite a number of estimations accumulated during January and February, 1918."

V.—Summary.

1. From the results of treating 1,040 old cases of malaria with anti-relapse quinine prophylaxis, it would appear that comparatively small doses, amounting to about 60 grains a week, distributed in various ways, reduce relapses to about 10 per cent. of the cases per month, and also diminish the severity of the relapses when they do occur—see, for example, treatments A 2, 4, 5. But 5 grains daily seem less effective—treatment A 1; and 15 grains daily are no more effective than 10 grains daily and less well borne by the patients—treatment A 3. The figures should be compared with the controls mentioned in Section 1, paragraph 9.

2. Treatments B, C and D, given to 1,420 cases, illustrate the difficulty of sterilizing cases entirely, but also seem to shew that success in this tends to vary directly with the magnitude of the daily dosage—see especially treatments C 15, 16, 17. No permanent bad effects with large dosage have been reported.

3. On the other hand, old cases generally do so well under treatment A that it is a question whether efforts to establish early and absolute cure in them by methods tried in treatments B, C and D are always very much worth while, especially as numerous cases under treatment A seem to recover by themselves, either completely or sufficiently to be able to return to light or full duty.

4. I cannot say that I have personally been able to note any marked superiority in any one of the three modes of administration of quinine—

oral, intramuscular or intravenous—as regards either the speedy reduction of the fever and the parasites (in relapses), or as regards complete sterilization of cases—see especially treatments B 10 and 13, and Section IV. Captain MEREDITH HARRISON'S method of using oral and intramuscular administration together is valuable when large dosage is employed—see treatments C 15, 16, 17. Very careful clinical and statistical work would be required to establish real differences in the exact results given by the various modes of administration.

5. Several of the medical officers favour complete rest in bed during treatment, even for two or three weeks, especially when large doses of quinine are being given. Generous diet and a little beer or wine are usually given—compare treatment B 6 *per contra*. Arsenic and iron are also favoured for the later stages of treatment, but it has not been possible as yet to obtain decisive statistical evidence in support of any of these views.

6. Out of the total of 2,460 referred to here, 682 or 27·7 per cent. are known to have relapsed either during treatment or afterwards.

* * * * * *

I regret that owing to my departure on duty from England to-morrow, I have not been able to complete this Interim Report as regards several particulars. I hope, however, to add details and to bring some of the treatments up to date in a subsequent note; and, as I have said, some of the medical officers concerned will doubtless furnish fuller reports of their results later on.

Captain F. W. O'CONNOR, R.A.M.C., has assisted me in the compilation of the Abstracts given above.

Postscript.

With reference to the remarks at the top of page 195 regarding the Aldershot Treatments C 15, 16 and 17, quinine was prohibited for all the 79 men examined by me in November, 1917, and every man was ordered to attend hospital weekly for clinical inspection, blood examination and record of weight. Only two of these men have relapsed since then. On the 25th-27th February, 1918, after my return from Salonica, I examined again 66 out of the 79 men and concluded that they were all now pro-

bably free from infection. The figures for Treatment C 15 and 17 have been amended accordingly.

With our present information, therefore, Treatment C 17 seems to be the best for resolving infections. R. R.

Discussion.

The Chairman: I think we may congratulate Sir Ronald Ross and his co-workers on the large amount of work they have done, if not altogether on the results they have attained. I will ask Sir William Osler to say something on the subject.

Sir William Osler: I am with you in your congratulations, sir, but not in your accompanying remark, for 2,460 cases with only 27·7 per cent. of relapses, during treatment or after it, is a good record, bearing in mind the type of malaria concerned. For we do know one or two definite things: and one is, that this type we have to deal with is an obstinate, I was going to say almost an interminable malady. It is a fixed conviction among many who live in badly infested regions that the malarial parasite is the "worm that never dies;" that persons once infected never entirely get rid of malaria. And there are certain points in favour of this view. Take the case of an individual who goes for six, eight, or more years with latent malaria infection and following an accident has an attack. On the well-established cases of post-mortem malaria, appearing long after the primary infection, just as with the *Spirochæta pallida*, which is an exceedingly difficult parasite to get rid of, so it is a question whether once infected the parasites of malaria may not remain in the body for many years after an apparent cure. I should say that in a very malarial district, as in one of the Southern States, if one collects the data of 2,460 cases, you would find many more relapses than are represented by the proportion of 27·7 per cent. I should not call that a very high percentage of relapses, considering the type of malaria. Rash statements always come home to roost, and after teaching medicine for a great many years one is apt to get dogmatic, and even to make foolish remarks. I have been quoted as both for maintaining that the man who could not treat malaria successfully with quinine should give up the practice of medicine. But I stick to it, only adding as a rider, "with time, in divided doses," for I should say that with quinine and

time all these cases get well. The cases I have seen—and through the kindness of Sir RONALD ROSS and his colleagues, I have seen a good many—may be divided into two groups, those patients without anæmia and without enlarged spleens who should not be in hospital but at work, and of course receiving treatment; and the cases with anæmia and large spleens which come into a different category, and demand long and careful treatment.

This is an admirable report, upon which Sir RONALD and his colleagues may be congratulated: and I would again remark that 27·7 per cent. of relapses should not be considered excessive.

Prof. J. W. W. STEPHENS: The few remarks I wish to make with regard to quinine treatment in simple tertian malaria, refer to treatments carried out with the object of obtaining a "cure."* These treatments may be divided into two groups: *(a)* those with moderate doses given over long periods—*e.g.*, two to three months; and *(b)* those with large doses for short periods, *e.g.*, two days.

In the first group the treatment may either be *continuous*, *i.e.*, daily or *interrupted*, *e.g.*, twice weekly. We have found that, whichever of these methods be used, it is only when the individual doses reach grs. 45 that a definite curative effect is obtained. There are 47 per cent. to 63 per cent. of cures in the case of *continuous* treatment, and 62 per cent. to 71 per cent. of cures in the case of *interrupted* treatment. This latter is preferable to *continuous* treatment, for the following reasons:—(1) The curative effect is equal to that of the *continuous* treatment; (2) the amount of quinine required in two months is grs. 720, as against grs. 2,520 per case; (3) the dose, grs. 45 twice weekly, is well borne, whereas many patients are unable to take a dose of grs. 45 daily for any length of time.

In the second group—treatments with large doses over short periods—we have found that the best result is obtained when the dose reaches grs. 90, the curative effect being 62 per cent.†

We recommend accordingly for the treatment of simple tertian malaria an *interrupted* treatment consisting of grs. 45 on each of two consecutive days weekly, for two months.

* By "cure" we mean no parasitic relapse in an observation period of 60 days after cessation of treatment.

† In a second series of 70 cases treated by this method, grs. 90 (on each of two consecutive days), practically all the cases relapsed within three weeks.

With regard to relapses of simple tertian malaria, whatever be the dose of quinine, and whatever be the mode of giving it, 95 per cent. of relapses will occur in the first month after cessation of treatment.

These conclusions are based on the treatment of some 700 cases. They are, in fact, a summary of the data which we have already published,* data based on the fundamental fact that *all our cases have been controlled by daily blood examinations.* The figures apply to simple tertian malaria only. How far they apply to malignant tertian malaria, parallel observations alone can shew. It is unscientific and so misleading to talk of the treatment of "malaria," for we have already made sufficient observations on malignant tertian malaria to convince ourselves that the reaction of the malignant tertian parasite (trophozoites and gametes) to quinine is very different to that of the simple tertian parasite.

Captain MEREDITH HARRISON: With regard to the treatment of malaria, I would like just briefly to tell you of the method I have used during the last ten years in the Federated Malay States for all types, whether benign tertian, quartan, or malignant. This is not less than 40 grs. of quinine per diem, either by intramuscular injection or orally or by the two methods combined. Usually four intramuscular injections of 10 grs. are given four-hourly, the first, as far as possible, at or before the onset of the rigor. After the four injections, 40 grs. are given daily in four doses by the mouth with strychnine, iron and arsenic for twenty-one days, during which period the patient should be kept in bed, and then twenty grains daily in two or four doses for a further period of from two weeks to one month—the duration of the treatment depending on the severity of the infection. For severe infections of the malignant type, intramuscular injections are usually given in 10 gr. doses, rising to 60 grs. in the twenty-four hours, and I have successfully given even as much as 120 grs. in the same period for two or even three days without ill effects. The above treatments I have given in many hundreds of cases with few, if any, relapses. These lines of treatment I have not found to succeed in cases of chronic malaria with frequent relapses, nor in patients who have for long periods been taking small daily doses of quinine prophylactically.

A short time before I left the Federated Malay States, I made three

* *Annals of Trop. Med. and Parasit.* 1917–18. "Studies in the treatment of Malaria." STEPHENS, YORKE, BLACKLOCK, MACFIE, COOPER, CARTER.

experiments on the question of prophylaxis on a certain estate there. This estate was quite isolated, and had its own hospital, and the coolies had but little chance of getting into the town. During eleven months I gave prophylactic quinine, and during that time, out of a labour force of just over 1,000, there were 640 cases of malaria, of mixed types. In this instance the death-rate among the coolies was 0·6 per cent., and the relapses very few indeed. In the next period of eleven months, during my absence on leave, my *locum tenens* carried out prophylaxis as follows:—grs. 5 was given daily to every coolie at the morning muster, and a similar dose at the evening muster, always in solution. During that time there were 650 cases, and the death-rate was 2·4 per cent., with three or four comatose cases. On my return I carried out a third experiment for a similar period, during which no prophylactic treatment was given on the estate. A competent dresser went to muster every morning, and if cases of fever were detected, the subjects were brought to hospital, their blood examined, and they were admitted if parasites were found. The number of cases during this third period of eleven months was 643, with a death-rate of 0·7 per cent. It has been my experience in the tropics that those who took quinine prophylactically and then contracted the disease, were far harder to treat than those who had not taken quinine.

Professor Warrington Yorke: I would much prefer to have had a month in which to digest this document before venturing to offer any criticism on it, but unfortunately it is not a simple matter nowadays to travel from Liverpool to this meeting, and hence what I have to say cannot be said at the adjourned meeting. I cannot pretend to have grasped the enormous and complicated figures in the paper, but I would like to refer to two points. The first concerns the use made of the word "relapse." In order to obtain any scientific information on the treatment of malaria, one must, I think, limit the use of that term "relapse" to the finding of the parasite in the blood: I am afraid that in this matter one cannot take cognisance of clinical symptoms. There are many conditions which clinically so closely resemble malaria that I am afraid I, at least, cannot distinguish them from malaria. One should always associate the presence of the parasite with one's statistical statements. At the end of Sir Ronald Ross's paper there is a table comprising 2,460 cases treated in a multitude of ways, in which the total

relapses are 682, a percentage of 27·7. Now, as it stands, this table is meaningless. No definite information can be extracted from it unless we know that a microscopic diagnosis was made in all cases and are informed, firstly, what was the length of the observation period: for how long were these people observed after the cessation of treatment? No doubt Sir RONALD ROSS will be able to supply that information at a later date. Secondly, we must know how often these people were examined, *i.e.*, their blood microscopically, after cessation of treatment. On going through the literature of this subject, one is impressed with the large variety of treatments which have been advocated. It is nearly forty years since LAVERAN'S great discovery; and the use of quinine, I suppose, has been known for 300 or 400 years, yet no one is even now able to state how the quinine should be taken, in what manner, and in what dosage. There are almost as many treatments of malaria as there are people who have written on the subject. This means, of course, that the people who have written on the treatment of malaria have, for the most part, not taken the precaution to see what happened as a result of their treatment. They have said, "We have treated so many hundreds of cases, and our impression is that they did very well;" or, "In our experience such and such a treatment is most valuable," and so forth. Post-impressionism of that kind is of no value. One has only to look at the two Provisional Instructions concerning the treatment of troops in this country, issued recently from the War Office, to see how utterly unsatisfactory our knowledge of the treatment of malaria is at the present time. One can judge of the value of the first instruction from the fact that it was superseded by the second after an interval of only four months. In the train to-day, I noticed on one of the hoardings that decorate the landscape, an advertisement of a certain patent pill, designated "Wait-and-See Pills." Unfortunately, it is only by this criticism that we can judge treatments for malaria: one must wait and see what happens before beginning to talk about the effect of any treatment. It is bad enough to recommend a treatment without trying to ascertain what its effect is; but when, without producing definite evidence in support of his contention, one records that such and such a treatment was given, and that his impression is that it is a good or a bad treatment, that is worse than useless, because it misleads other people, and so prevents progress.

[*Adjourned to the Third Friday in March.*]

Proceedings of a Meeting of the Society held on Friday, March 15th, 1918, at 5.30 p.m., at 11, Chandos Street, Cavendish Square, W.1, Surgeon-General Sir David Bruce, K.C.B., F.R.S. *(President)*, in the Chair.

ADJOURNED DISCUSSION ON THE TREATMENT OF MALARIA.

Colonel S. P. JAMES, I.M.S.: Since the last meeting of the Society most of us have had the opportunity of studying in detail Sir RONALD Ross's "Interim Report on the Treatment of Malaria"; and most of us, I am sure, have come to the conclusion that it gives very valuable assistance in deciding what is the best method of using quinine for the treatment of the disease. The value of the report lies as much in the unsuccessful as in the successful results recorded. It is usually stated in text-books that quinine is an infallible remedy for malaria; but those who have had most experience in using the drug are well aware that, while this statement is true as regards the cure of the clinical symptoms of an attack, it is by no means true as regards the destruction of all the parasites which an infected person harbours. And, for this reason, they are aware that the drug is not infallible in protecting against relapses. On this point, especially, the report affords confirmation from the clinical side of the correctness of observations made from the protozoological side. Some of the most important researches in connection with the action, and failure of action, of quinine upon different forms and stages of the malarial parasite, were made by MACHIAFAVA and BIGNAMI more than a quarter of a century ago; and their observations have since been repeated and extended by workers in Italy and India. It seems to me that at the present time it ought to be possible, from a knowledge of those researches and of the results recorded in the present report, to summarise in a useful manner what we know of the limitations of quinine for the treatment of malaria, and to lay down a few rules that would be of service to those who are in doubt as to prevailing opinion regarding the best routine method of administration and dosage. My own ideas as to the headings for a summary of this kind would be somewhat as follows:—

(1) Quinine still remains the only known drug that has a true specific action on the malaria parasite; and the failure of antimony and various arsenical preparations has, I think, been proved.

(2) When quinine can be given by the mouth, and can be absorbed by that route, its action is as effective as when it is given either intravenously or intramuscularly : and it should be given by those routes only when it cannot be given by the mouth.

(3) The subcutaneous injection of quinine is not justifiable.

(4) As regards dosage, the report shews clearly, I think, that large doses of quinine are not more effective than moderate doses; and that if large doses are continued for more than a very few days their action is decidedly harmful. Major J. B. STEPHENS has gone into this matter carefully in connection with what was called the "intensive" method of treatment at Epsom, and I hope he will record the results in detail.

(5) Summing up my personal view as to the best method of treating the cases of malaria that come home, and are not subject to new infections, I think that the treatment of the actual attack or relapse should be limited to about 30 grs. of quinine daily for not more than five days, and that the "after treatment" should preferably be an intermittent one of, say, 30 grs. every Sunday, or, if a daily one, that the daily doses should be small, and should not in any case exceed 10 grs.

(6) We are not at present concerned with the use of quinine for protection against new infections, except to state without ambiguity that the best methods of using quinine for that object are entirely different from the method just mentioned.

In the present discussion I think it would be useful if speakers would state their opinions and experience in the same didactic manner as I have attempted to do. If they will do so, we may be able afterwards to correlate and summarise our views in a manner that will serve as a useful guide to those who wish to know what is the prevailing opinion regarding the best method of employing quinine for the treatment and "after treatment" of malarial patients who come home from the Eastern Fronts.

Similarly it would be very helpful if opinions could be summarised as to what further lines of research should now be undertaken. We are all aware that very little is known not only about the action of quinine on different stages of the parasite, but about the exact history of a dose of the drug in the human body. It seems likely that better methods of using quinine might be devised if we had an intimate knowledge of this subject; and I think that members of this Society ought not to shrink

from the responsibility of assisting to set out a scheme of investigation with that end in view.

Major J. B. STEPHENS: As regards the first point which Col. JAMES mentioned, that is, the inefficiency of drugs, other than quinine, my experience at Epsom absolutely tallies with his. We found that antimony and arsenic did not give results at all hopeful for sterilising the blood.

As regards the intravenous and intramuscular medication, too, the results in the majority of cases shew that they are in no way preferable to oral administration.

The first method of oral administration which we tried at Epsom was one which we called, for want of a better name, the intensive method. This method consisted in giving the sulphate salt in an acid mixture: for the first week, 10 grs. three times a day; the second week, 12 grs. three times a day; the third week 15 grs. three times a day. At the end of three weeks the quinine was stopped. The total number of cases treated in this way was 193, and during the treatment 18 of these relapsed. Therefore the percentage of relapses to treated cases was 9·3 during the time they were having doses of quinine of not less than 30 grs. a day. One hundred and seven of the cases relapsed before they left the hospital and one was known to relapse afterwards, so that the percentage of relapses to total cases treated was 59. A large number of the cases left the hospital shortly after the termination of their treatment, and as the majority of relapses occur in the second and third week after treatment, it is to be presumed that a large number of the 68 cases who went out without having a relapse in the hospital relapsed in the second or third week after their discharge.

Of the relapses, one was with parasites only, eight who did not have their blood examined, relapsed with fever, one relapsed with parasites and no fever, three with parasites and fever, and five with fever and no parasites; three of these, however, were cases of hæmoglobinuric fever. It is perhaps unfair to class these as malarial relapses, but they were included in an original series, so I have included them here. The earliest relapse recorded was on the fourth day of treatment. There were six relapses during the first week, eight during the second week, four during the third week. Two cases relapsed twice.

One case in the series is interesting. This man was taking 15 grs.

three times a day. He relapsed on the 6th, 8th and 10th days. Fever left him. There was no alteration in the quinine treatment, but the blood remained positive to the end of the treatment. The quinine was then stopped and the blood continued positive for a further 14 days. At the end of that time he had a fever relapse, and his blood remained positive. He was put on five grains of quinine by the mouth; the parasites and fever disappeared, and for the remainder of his stay in hospital he was free from fever and parasites.

With regard to relapses after treatment, there were 12 in the first week, 47 in the second week, 29 in the third week, 9 in the fourth week, 5 in the fifth week, 7 in the 6th week, so that the majority of the relapses were in the second and third weeks. A large number of patients were sent out of hospital before the time at which relapses were to be expected.

The other treatment which we have gone in for fairly extensively has been to control the initial fever with 10 grs. three times a day, and then putting the man on to 10 grs. of sulphate of acid mixture daily. I would have preferred to have followed the method Colonel JAMES suggested, that is, intermittent treatment with quinine, but in dealing with men in the army, one has to have a more or less cut and dried scheme, in order that it may be followed not only in the hospital, but also outside it. For that reason we put them on 10 grains daily, to see what happened. The quinine was given in an acid mixture at 11 o'clock in the morning, at quinine parade, and every endeavour was made to see that the men actually swallowed the quinine; after taking the quinine into the mouth they were required to say their name and number. Four hundred and forty-six cases were treated in this way. I have been able to scrutinise only 310 of these cases; they are not selected cases, and I think the figures I give for the 310 will work out more or less equably for the total number. These 310 cases stayed in the hospital 13,734 days, or an average of 44·3 days' stay. Twenty of the cases relapsed, which gives a percentage of about 6. These relapses were decidedly mild, so mild that the total number of days of fever works out in them at not more than two days per relapse during the course of the quinine treatment: in other words only 40 days out of a total of 13,734 days.

Captain MURRAY: I am able to bring up to date some of the figures in the report presented by Sir RONALD ROSS. I will refer to the para-

graphs of the report. Page 185, paragraph 4: the cases up till the end of February are 16, of which 13 relapsed.

The two important results which I wish to note now are, page 191, paragraph 8: 49 cases treated by hydrobromide of quinine, of which 16 have relapsed to date, making a percentage of 32·6.

In the next page, paragraph 20, there are now 143 cases; that is, 30 grs. of quinine, either sulphate or hydrochloride, 10 grs. three times a day, given over three weeks, followed by prophylactic quinine, 60 grs. a week for two months. Thirty-six have relapsed, giving a percentage of 25·2. Hydrobromide is shewn to be an inferior salt to sulphate or hydrochloride. That is the only important point I want to bring out in these figures now.

Colonel JAMES has asked us to give our general opinion; therefore I will make a few remarks on the general treatment of malaria.

1. I must first bring the figures from the London Hospital up to date, *i.e.*, to 28th February, 1918.

2. I think we must recognise that, in dealing with war malaria, we are up against a different problem from that we meet with in the ordinary tropical practice. The infection is, in many cases, very heavy, and the strain and hardships to which some of the men have been subjected, have reduced their resisting power. In fact the conditions are somewhat similar to what obtain in coolie camps on railway and other engineering works in the tropics.

3. One point which we have noticed at the 4th London General Hospital is the small number of *Plasmodium falciparum* infections, compared with those of *P. vivax* (about 5 per cent. only). The figures I have from Salonica give a percentage of about 26 per cent. cases of *P. falciparum*. This indicates that *P. falciparum* is more easily eradicated than *P. vivax*, and this is borne out by a series of cases which we have had. They came in shewing *P. falciparum*, were treated and the blood became negative, and then they relapsed, and the blood now shewed *P. vivax* (we have had about a dozen such cases). It would, I think, be a help if in future reports the different infections were separated.

4. A further point to be considered is the final results as regards the general condition of the patient. It is no good saying you have cured the patient because there has been no relapse if the man is useless otherwise. We find a large proportion of the cases are suffering from some

form of D.A.H., and sometimes definite dilatation. Twenty-nine out of the last 71 cases on my register shewed some abnormality. I am collecting material from this point of view to see if something can be formulated as regards prognosis. Dr. JAMIESON is working at the blood pressures with a similar view.

Then there are the neurasthenics and the men suffering from chronic hospitalism, and to save these cases one would welcome a short sterilising treatment. With regard to the Aldershot treatments, Nos. 15, 16 and 17 in the report, these are the most promising, but they are severe, and the figures are, to some extent, vitiated by the fact that many of the patients would appear to have had prolonged prophylactic treatment after leaving hospital. One speaker (Captain HARRISON, I think), brought forward figures from the Malay States, shewing that prophylactic doses of quinine were valueless. My experience is different. When I had charge of Chittagong Jail, I examined as a routine measure the blood of every convict who entered. During 1916, there were in round numbers 800; of these about 20 per cent. shewed parasites in some form in their blood. According to the Bengal Jail code they all received 15 grs. of sulphate of quinine every Sunday and Monday, and during the year the number of attacks of malaria in the jail was 8.

When we come to speak of heavy dosage as recommended by Colonel STEPHENS and Captain HARRISON, the following figures furnished me by Dr. NIERENSTEIN are interesting. Of 74 cases examined, 55 were taking 30 grs. of quinine or less daily, and in 3, *i.e.*, 5·4 per cent., of them albumin was found in the urine. Nineteen cases were taking over 30 grs. daily, and in 15, *i.e.*, 79 per cent., albuminuria was present. At the same time we propose to try these methods and have already made a beginning, though, so far, with not very encouraging results, but a report will be furnished in due course.

As regards prognosis, I am inclined to think that the probability of relapse might be expressed in terms of the number of parasites found in the peripheral blood. This will require working out, and many parasite counts will have to be made—a very laborious process.

The PRESIDENT: You had 800 men in the jail and you gave them all quinine? You did not give 400 quinine and let 400 go without?

Captain MURRAY: No, we were not allowed to.

The PRESIDENT: In Africa we would find parasites in the blood of every native, yet I never saw the adults among them suffer from malaria. The presence of the malaria parasites in the blood would not mean that these people were going to have malaria, would it? It did not mean that in Africa.

Dr. NIERENSTEIN: My contribution to the discussion on the treatment of malaria can only be of an indirect character, as I have been carrying out a biochemical investigation on the excretion of quinine in the urine. My results up till now can be summarised as follows:—

(1) That there is no difference in the excretion of quinine sulphate, hydrochloride, bihydrochloride and hydrobromide. Some differences have, however, been noticed in a few experiments carried out with quinine lactate, the free quinine alkaloid and euquinine.

(2) That there is no difference in the excretion of quinine if given orally, intramuscularly, intravenously or in a combination of oral and intramuscular treatment.

These results are summarised in Table I., which deals with 74 cases examined by me.

TABLE I.

	Oral.		Intravenous.		Intramuscular.		Intramuscular and Oral.		
	Cases.	Av. %	Cases.	Av. %	Cases.	Av. %	Combination.	Cases.	Av. %
Quin. sulphate ...	23	51·72	—	—	—	—	Bihydrochloride & hydrochloride.	—	—
,, hydrochloride...	11	54·16	—	—	—	—		—	—
,, bihydrochloride	11	56·82	3	57·60	5	56·60		2	54·49
,, hydrobromide...	9	55·50	—	—	—	—	—	—	—
,, lactate	4	40·00	—	—	—	—	Bihydrochloride & sulphate.	—	—
,, alkaloid ...	2	34·00	—	—	—	—		—	—
,, euquinine ...	2	24·38	—	—	—	—		2	55·10

(3) That there is a tendency for the excretion of quinine in the urine to reach a maximum concentration of 6 to 11 grains per litre of urine.

(4) That a higher concentration of quinine per litre of urine produces albuminuria.

These results are summarised on Table II., dealing with a total of 1,539 analyses carried out by me.

TABLE II.

Grains of quinine base, per litre of urine.	Frequency.		Albumin.	Grains of quinine base, per litre of urine.	Frequency.		Albumin.
1	8		0	15	37		32
2	6		0	16	34		18
3	6		0	17	27		27
4	3		0	18	17		16
5	29		8	19	17		17
6	349		22	20	32		32
7	97		4	21	19		19
8	95	73·68 %	6	22	22		22
9	158		14	23	32		32
10	89		8	24	9		9
11	346		22	25	6		6
12	76		36				
13	34		14		1539		
14	37		22				

(5) That it is not advisable to give higher doses than about 30 grs. of quinine, and that if higher doses are required it would be advisable to increase the amount of fluid imbibed as suggested by Colonel Sir RONALD ROSS.

The fact that we reach a maximum of concentration of quinine in the urine, suggests that there must be a corresponding maximum concentration of quinine per litre of blood, since according to MICHAELIS $\frac{Cb}{Cu} = K$ as observed by him in the case of NaCl, NaBr, etc. I am not a medical man, and my suggestions must therefore be entirely of a tentative character, but it seems that if it were possible to increase the concentration of quinine in the blood stream we might have a way of increasing the effective proportion of quinine and its activities on the parasites. The concentration of quinine in the blood could be increased by increasing the acidity. That, perhaps, would not be physiologically safe. Or it could be done by increasing the urea content of the blood, since the ureate of quinine is a very soluble product, and since also there is the probability that quinine circulates as the ureate in the blood stream. Those, briefly, are my results as they stand at present.

The PRESIDENT: Have you made examinations of the blood from them?

Dr. NIERENSTEIN: No, sir, I have not.

Sir RONALD ROSS: I thank Colonel JAMES for his remarks about this army paper. The one which was circulated before was only a proof, not corrected: since then, I have corrected it. I want to apologise for not having given everybody here a copy of the corrected report, but unfortunately the printer has not sent it in time.

I would like to explain that it is very difficult for a man to collect and collate and verify results like this, given by more than a dozen workers, many of whom are changing, and all of whom are singularly modest gentlemen, so modest that they will not publish their reports themselves; and it has been a serious business to abstract their reports. I hope I have got all the details as correctly as possible; they have been given to me in writing, and they have been verified as thoroughly as I can verify them.

There is only one point of importance which remains. Those who read this interim report, and those who have spoken to-day, have specially referred to the Aldershot treatments, invented and used by Dr. MEREDITH HARRISON, who, I am sorry to say, has left the R.A.M.C. (though he is here this evening). As you will see from page 193 these treatments consisted of a very large dosage, given partly intramuscularly and partly orally. I saw a number of men undergoing this treatment, up to 100 grs. a day; I saw them in bed, and satisfied myself that they were not suffering in general health from the treatment.

Last November I went to Aldershot, and determined to see as many of these cases as possible after they had left hospital. I saw, as I say in the note on page 195, nearly 80 of them. I talked to each man, and Captain MEREDITH HARRISON was present at the time. We found that, unfortunately, by some mistake, these men were being given small doses of quinine by the medical officers of their units after they had left hospital; they had been treated by Captain MEREDITH HARRISON at the hospital, and the medical officers ought to have been informed that they should be given no more treatment, but that they should be watched to see how many had relapses. The fact that they were being given 5 grs. of quinine a day, of course, vitiated the experiment. To the corrected report I have added a postscript. Directly I knew the above facts, I ordered that none of these men were to be given quinine subsequently to my investigation last November, and that each man was to come to the Connaught Hospital to be examined once a week, to be weighed, to have his blood examined, and to have a clinical examination. This was

*NOTE *added* (*p.* 215) *May* 15*th*, 1918.—I have been asked whether I definitely adopt and recommend the high dosage treatments. All I said in my paper and other remarks was that the high dosage treatments appeared from the statistics to give the best results up to that time as regards stopping relapses. But, as I noted in par. 3 of the Summary of my Interim Report, I am very doubtful whether a simple anti-relapse prophylaxis is not, for general reasons, more worth while adopting in the majority of cases than any treatment now known to us which is aimed at establishing an absolute cure straight away.

carried out in the two or three months I was away in Salonica. When I returned from there at the end of last month, I again went to Aldershot and examined as many of them again as possible, namely, 65 of them, at the end of February, and we found that only two of the men had relapsed in the interval. I saw the men, who looked remarkably healthy; there was no sign or evidence that they any longer had parasites in their blood. They certainly looked better at the end of February than they had looked in November last, and Captain MEREDITH HARRISON had been examining these men steadily every week, and therefore I think you can rely upon the report that the treatment given was very effective. The treatment, I think, has given the best results that we have obtained in the four commands*.

As regards sterilising patients entirely, the treatment which he told me he liked best was C17, on page 193, the patient being kept in bed all the time. I have put in a paper, which I do not think I need read, detailing the whole treatment. Perhaps he will add some more details. I am circulating this paper too, and giving it for the TRANSACTIONS.

I was very glad to hear the good results mentioned by Major STEPHENS on the anti-relapse prophylaxis, as I call it; that is a continuation of the anti-relapse prophylaxis mentioned in the Interim Report.

I have recently received a very interesting document from the D.M.S., Salonica, giving the results of enquiries on the treatment of malaria, which he has made among a large number of medical officers serving there, all of whom have constantly been treating malaria cases and supervising quinine prophylaxis. I am allowed to give the following brief summary of the opinions expressed by these medical officers on various points at issue:—

(*a*) The Medical Officers were asked for their opinion regarding the value of 10 grs. of quinine given twice a week as a prophylactic measure. Out of 111 officers who have expressed definite opinions, 2 stated that this dosage of prophylactic quinine is of great value; 2 stated that it is of definite value; 10 stated that it is of some value; 18 that it is of little value; 72 that it is of no value; and 7 that it is of no value and objectionable, because it renders the parasites immune and masks the symptoms. One officer said it was of use against benign tertian and not against malignant tertian. Five officers thought that the minimum dose of any prophylactic value should be 10 grs. daily. In addition to these 111 reports, 4 officers confessed to being uncertain. Thus out of the 111 officers, 71 per cent.

* See slip.

considered that 10 grs. of quinine given twice a week as a prophylactic measure are of no value or are objectionable.

(*b*) The officers were next asked to give their opinion regarding the optimum dosage for treating relapses of malaria in Regimental Aid Posts, where patients are under treatment for a period not exceeding 3 days (patients whose fever exceeds that period being sent further back). Out of 111 officers who expressed definite opinions, 1 advised 80 grains of quinine daily; 6 advised 60 grs. daily; 13 advised 45 to 50 grs. daily; 14 advised 35 to 40 grs. daily; 70 advised 30 grs. daily with subsidiary treatment; 4 advised 20 grains daily; and 3 objected to any optimum dosage, but thought that each case must be treated on its merits. Thus the large majority of the officers, namely, 63 per cent., are in favour of 30 grs. daily—though 4 advised an increase of 45 grs. daily if necessary, and 1 advised 15 grains every 4 hours until the temperature falls.

(*c*) Asked what is the optimum dosage for recurrent cases of malaria now doing duty after they have been kept in Regimental Aid Posts for a few days, 107 officers report as follows:—Nine recommended the complete stoppage of quinine unless relapses occur, the treatment being confined to arsenic, iron and other tonics. Seventy-three recommend that fixed doses of quinine should be given for periods varying up to $3\frac{1}{2}$ months; and of these 73 officers, 26 recommend 10 grs. daily, 21 recommend 20 grs. daily, and 26 recommend 30 grains daily. But 25 officers recommend graduated courses under which the quinine dosage is reduced as the course progresses. Three officers recommend 30 grs. daily for 10 days, followed by 20 grs. daily for another 10 days. Ten officers favour 30 grs. daily for 1 to 3 weeks, followed by 20 grs. daily for 1 to 3 weeks, and 10 grs. for the remainder of the course of 3 to $3\frac{1}{2}$ months. Five officers recommend 10 to 30 grs for 2 to 4 weeks, and then 5 grs. daily. The remainder of the 25 officers suggest various other lines of treatment.

(*d*) Asked what is the optimum dosage for recurrent cases of malaria on return from hospital, out of 105 officers, 16 recommended the complete stoppage of quinine unless relapses occur. Sixty-five officers advise the same daily dose of quinine given for various periods. Of these 33 advise 10 grs. daily for from 1 to $3\frac{1}{2}$ months. Twelve advise 20 grains daily for similar periods and 16 advise 30 grains daily. Thirteen officers advise various courses of treatment in which there is a gradual reduction of the quinine as the course progresses.

Subsidiary treatment is of course recommended by many officers. Others suggest the continuance of the quinine until the end of the malaria

season ; and others make numerous suggestions which cannot be included in a summary like this.

Treatment C, 17.

1. Apparently the best treatment for old cases of malaria which has yet been used in the Southern, Eastern and Aldershot Commands, and London Districts (at least to judge by the small number of cases which are known to have relapsed after the treatment was given), has been treatment C, 17 (recorded in my Interim Report on the treatment of malaria, finally dated 4th March, 1918, 24/General Number/ (A.M.D. 2.) /6198), devised by Captain MEREDITH HARRISON, R.A.M.C., in charge of the malaria cases at the Connaught Hospital, Aldershot. This treatment was used by him between the 10th July and the 6th October, 1917, for 49 chronic cases of malaria, mostly of benign tertian, and mostly arrived from Salonica. Of these only 5 had relapsed after the cessation of the treatment in October until the end of February, 1918, when I inspected a large number of cases. It may be added that three quarters of these cases have been examined since their original treatment at the Connaught Hospital once a week as regards their clinical condition, their blood, and their weight ; and as most cases of malaria in the Aldershot demand are closely in touch with the Connaught Hospital, I think that the number of cases which relapsed given above is accurate. The percentage of cases relapsing, as given by these figures, is therefore only 10·2 per cent. The time which elapsed between the end of the treatment and the beginning of the relapse (in the 5 cases which did relapse) varied from 16 to 72 days, and averaged 34·5 days. Captain HARRISON reports that with this treatment the fever was reduced within from 12 to 24 hours, and that no asexual parasites could be found after 48 hours. The effect of the treatment as regards general improvement of health was good. The treatment was well borne by the patients except for deafness and tinnitus, and there was very little vomiting. But the patients always object to stopping in bed for 12 days.

2. The treatment was as follows :—The patient is put to bed for 12 days and given daily the following treatment for all this period, namely, grs. 15 of the bihydrochloride of quinine intramuscularly in each deltoid muscle, together with grs. 10 of hydrochloride of quinine in mistura anticachexia No. 1 thrice daily—totalling 60 grs. of quinine daily for the 12 days. After this the patient is allowed up and is given mistura anticachexia No. 2 four times a day, that is, 60 grains of quinine daily by the mouth, this treatment being continued for 3 days. After this the patient is given mistura anticachexia No. 3 four times daily for 14 days—that is, 20 grs. of quinine daily, the patient being allowed to do light work all this time. Captain MEREDITH

HARRISON'S prescriptions for mistura anticachexia No. 1, No. 2, No. 3, are appended below.

3. It will be useful if medical officers in charge of malaria cases would follow this treatment exactly as laid down by Captain MEREDITH HARRISON and report the results as regards relapses to me.

MISTURA ANTICACHEXIA No. 1.

Quinin. hydrochlorid.	gr. x.
Tinct. ferr. perchlorid.	m. v.
Liq. strychn. B.P.	m. v.
Liq. arsenic. hydrochlor.	m. v.
Acid. nitrohydrochlor. dil.	m. v.
Magnes. sulphat.	dr. ss.
Syrup. tolut.	dr. ss.
Glycerine	m. x.
Aquæ ad	oz. i.

For a dose, to be given as directed, after food.

MISTURA ANTICACHEXIA No. 2.

As No. 1 but add—

Quinin. hydrochlorid.	gr. v.
Acid. nitrohydrochlorid.	m. v.

to the dose.

MISTURA ANTICACHEXIA No. 3.

As No. 1 but reduce—

Quinin. hydrochlorid.	gr. v.
Acid. nitrohydrochlorid. dil.	m. v.

in each dose.

Professor W. J. SIMPSON: It would be interesting to know where the 75 per cent. of medical officers were located who came to the conclusion that quinine was practically of no use at all as either a prophylactic or as treatment, because the situation is very different in different parts of the world. Some parts are extremely malarious where the soldiers are, and if they are sent back to these parts they are likely to be reinfected, and in that way to have relapses. Further, I have not seen in the hospitals where the cases were treated any very serious attempt to have them so screened that there should not be reinfection going on in the hospitals themselves.

As regards these large doses, I met one medical man who gave large doses, but he also combined the drug with strychnine, and that seemed to me to be a precautionary measure, which indicated that there was some idea of danger attaching to the giving of large doses. One would like to

be sure whether some of the cases of heart failure that sometimes occur were caused always by the malaria parasite itself or by the very large doses of quinine. I have seen a number of cases of heart failure in this connection where I felt that possibly the dose was rather large for the man, and that the large dosage might be the cause of the failure. For myself, I prefer smaller doses, and I think those who have lived a good deal in the tropics, and been connected with the treatment of malaria cases, do prefer these small doses. Even in England there have been cases reported—I do not say they have been in the Army—where, by accident, a large dose—say, 90 to 100 grs. of quinine—has been taken, with results that have been almost fatal. In 1914, Dr. GIMLETTE records cases in the *Lancet* in which 90 grs. of quinine were taken by three Chinamen, which proved fatal to two and made the third seriously ill.

With regard to the statistics brought forward in the report, I think a very important matter—possibly it has been done—is to differentiate and classify them according to the localities from which the cases come, because we know very well in the case of malaria, as with many other diseases, the locality has much to do with the intensity or severity of the disease; and if all these cases are lumped together, *i.e.*, those which come from a place where the disease is very intense and those from a place where it is mild—for in the latter the cases are very amenable to quinine and there is no relapse—we shall not get such helpful results from the figures. We should also know the type of malaria that is being treated, and the types should be kept separate in the statistics. If that has been done, it will be interesting to know what the result of this grouping is.

Lieut.-Colonel R. H. ELLIOT: My interest in the subject is entirely from one side, namely, the side of its dangers. During the past month I have been through the whole of the literature—both British and foreign—concerning quinine blindness, both amaurosis and amblyopia. I do not wish to exaggerate the dangers of giving quinine in the least, but the number of unfortunate cases published is very considerable.

The dose of quinine is influenced by the particular salt used, by the vehicle employed, by the method of giving it, by the total bulk of it which is retained, by the idiosyncrasy of the patient, and by his age and weight. I want to speak very shortly on two or three of those points.

Dr. NIERENSTEIN suggested combining quinine with urea, to increase its solubility in the blood serum. That has been done by DE SCHWEINITZ in experiments on dogs, and he has intensified thereby the cinchonism of the blood. One of DE SCHWEINITZ'S strong points in his work on toxic amblyopia is that one of the most dangerous of all the drugs is the carbamide of quinine, made by the combination of muriate of quinine with the carbamide of urea.

With regard to the age and weight of the patient, these are factors of great importance. Right through this literature, one thing that strikes one is the danger of giving young, *i.e.*, small, people quinine. You have to watch the weight of the drug in relation to that of the patient in each case. DE SCHWEINITZ brought that out strongly in his work on dogs.

The real danger-point, however, is the idiosyncrasy of the patient. I have, as I say, no wish to exaggerate the risks; it may be that the end justifies the means, and if in order to cure the malaria you must give large doses of pure quinine, then you must give them. But I want to raise a note of warning, for if you cure the malaria and leave your patient blind, he will not thank you. Indeed, he might prefer that you should have left him to die of his disease. Following the ingestion of quinine, amaurosis, *i.e.*, total blindness for a certain time, sometimes occurs; this, in turn, is often followed by quinine amblyopia. Even though the patients recover from the amaurosis, you will leave a certain number of them with restricted visual fields, and with a modified form of amblyopia hemeralopia; they will stumble in the dusk and in the semi-darkness, and altogether they are considerably worse off than before they had the drug. If you are going to give these people quinine, I think you should employ some form of perimeter and take the visual fields—a perfectly easy proceeding, as is also the other requisite, viz., electrical ophthalmoscopy, in order to watch for pallor of the optic disc and constriction of the retinal vessels. If you do, I think you will find a number of your patients suffering from some form of quinine poisoning, and possibly a much larger number than you guess.

One speaker to-day has brought forward the question of deaths from quinine, mentioning that of the three Chinese coolies who took 90 grs. each and only one survived. There are people who have been dangerously ill after taking much smaller doses (2 grs., 8 grs., 30 grs., etc.), whilst other fatal cases are on record from comparatively low doses.

I do not deny that idiosyncrasy to the drug plays an important part in such cases. Anyway, there is abundant evidence in the literature that the cardiac failure was in some cases due to the quinine and not to the disease.

In a large number of cases of amaurosis you will find there was collapse and heart failure before any complaint of blindness; changes in the pulse and unconsciousness are also noted. If there is a prospect of experts in tropical disease enlarging their dosage of quinine, I think it is essential to have continual regard to this point.

I may be asked, as one who has worked a good many years in a tropical climate, how many cases of quinine amaurosis I have seen. I reply that I have seen four certainly, possibly a fifth. But my work has been in the Presidency of Madras, which was the first centre of education in India. There the medical men are very careful about their dosage, and even though quinine is sold from the post offices, it is very rare to hear of really large doses. As I have said, I saw only four or five cases there, and KIRKPATRICK has since published one case. I will give you a series of doses which have proved toxic, taken from the available literature:—MYERS, with 120 grs., a young female aged 20; GIMLETTE, with 90 grs., three Chinese coolies; KALEBAIKIN, 80 grs.; CLAIBORNE, 60 grs.; VON SPEYER, 60 grs.; WEEKS, 60 grs., a child aged 6 years; BEIDLER, 40 grs.; KAZ, 40 grs.; FORTUNATI, 45 grs.; CARGILL, 30 grs., a young woman; NETTLESHIP, 22 grs., a male aged 26; SCHWABE, 19-29 grs., a young woman of 33; BERANDI, 15-20 grs., in experiments on healthy subjects; DE SCHWEINITZ, 15 grs.; H. C. WOOD, 12 grs., a woman; TYSON, 10 grs.

Some of the worst cases on record are those in which the patients took the drug in whisky, in which it is very soluble. KEIPER'S case was permanent with 120 grs.; HARBRIDGE'S was permanent with 60 to 120 grs; also WELTON'S with 55 grs. and M'GILLIVRAY'S with 40 grs. After being given in limejuice, 120 grs., MYER'S case, too, sustained permanent damage. LAVERAN recommends that the dose of the hydrochloride should never exceed 45 grs. daily, and BALDWIN thinks 60 to 80 grs. a poisonous dose.

Another point I will make is the danger of repeated doses, especially if there has been previous severe cinchonism. Under such circumstances, even with 10 to 20 grs., there may be a marked increase in the ambly-

opia. The most remarkable case was one of SCHWABE'S. The patient had a large dose of quinine and got quinine poisoning—she was a working woman in New York. Subsequently she drank strong coffee, and every time she took coffee she had definite amblyopia. Whenever she took strong tea or coffee she shewed pallor of the optic nerve and shrinking of the retinal vessels, with limitation of her visual field. The trouble reached its maximum in one hour and passed away in two hours. This led SCHWABE to utter the obvious warning, which has been expressed also by a number of other writers, to be careful in such cases. I have no wish to be an alarmist, but I do desire to draw the attention of this meeting to the possible danger of large doses of quinine salts.

Captain D. THOMSON: I have not anything to say with regard to the proper dosage of quinine necessary to cure malaria. It seems to me, however, that what is lacking, in all the work which has been done on this subject, is a definite method of ascertaining when a patient is free of the disease. The only means we appear to have at present is to allow the patient to go away, then to keep in touch with him and see if he has any relapse. We need to develop some better test whereby we may know whether any patient is free of the disease. I think such a test could be developed on the lines of the Wassermann reaction. We have now developed a very reliable complement-deviation test for gonorrhœa on the same lines as that for syphilis, and this test is more reliable for latent cases than the clinical diagnostic methods. I think we should try to work out a similar complement-deviation test for malaria. The treatment of syphilis is now always controlled by the Wassermann test. With regard to specific disease, the Wassermann test has brought out the tremendous importance of catching the case early and treating it at once. If treated almost as soon as the disease is contracted, or, at any rate, soon after the first appearance of the chancre, there will be some 90 per cent. of cures or more. If even fourteen days' delay occurs, the cures may drop 20 per cent. If delayed one month or two months, perhaps only 50 per cent. can be cured; and if treatment be delayed for six months, a definite cure may be impossible. If such a test could be brought out for malaria, it would enable us to know how long to continue with the quinine, and also it would be possible to find out if, as in the case of syphilis, it is important to treat malaria at once and treat it thoroughly.

Major F. CHARLESWORTH: I have no statistics to offer on this occasion, and a good deal of the ground that I did propose to traverse has been so fully covered by other speakers, that I think there is not very much left that I can usefully add.

I regard this paper of Sir RONALD ROSS's from two points of view. One is that of its practical usefulness. Large numbers of medical officers who are now being brought into contact with the treatment of malaria, will find it extremely satisfactory and of a great assistance to have a definite line of treatment suggested. I might say, roughly, on the results arrived at, that moderate doses continued over a substantial period is, in the experience of most medical officers who are acquainted with malaria, especially in the tropics, the one most likely to yield successful results. The question of these enormous—and in many cases I should call them frantic—doses of quinine has been fully gone into, and I am very largely in sympathy with the criticism against giving those large doses. One sees papers published in leading medical journals giving the experience of medical officers. One paper I call to mind, of a series of what is termed "cerebral malaria," and in reading that article it seemed to me that symptoms of cerebral malaria did not arise until enormous doses of quinine had been given. There were one or two necropsies in connection with that series, and one was reported in which grey hepatization of the lung was found which had, apparently, given rise to no clinical symptoms, and was not considered to have any connection with the illness or the death.

I was not able to follow Colonel STEPHENS' remarks with regard to large doses of quinine in his intensive method, because he defines cure as being one in which no *parasitic* relapse occurs over a period of two months; and I understand he ignores any relapse with malaria symptoms—fever, etc.—in a case where the parasites are not discovered. That point of view may be used in scientific research for the purpose of statistics, but it seems to me, in practice, that if you have a series of cases in which the malaria parasite has been found early and in which, under quinine, you have further attacks resembling those of malaria, and not ascribable to another cause, and you do not find parasites present, I do not see how you will deal with that case, unless you regard it as a real relapse. Sir WILLIAM OSLER, in referring to the series of 2,500 cases which are published here, said he considered the proportion of 27·5

per cent. relapses as satisfactory, or rather, that the rate compared well with his experience in America. The results, therefore, obtained by the method of treatment advocated, which give only 10 per cent. of relapses is encouraging, viewed from the basis on which these investigations were made.

I pass from that point of view, and would not at this late hour refer to the other from which I wish to discuss the subject of this report, had it not been brought forward by Lieut.-Colonel Elliot. The series of treatments given in this paper constitute a bewildering series of figures and variety of methods of treatment—not based on any definite principle or knowledge which would have led to the anticipation that any one method was likely to give better results than another.

The point I wish to suggest is this: that we have in connection with malaria, certain facts of the greatest importance, which, though recognised, have not, so far as I am aware, been investigated, but whose investigation may lead us to more certain ground with regard to prevention and cure.

The facts to which I allude are those connected with immunity; the known facts are, so far as I am aware, at any rate, not numerous, but they are suggestive. The comparative immunity acquired in time by residents newly introduced into a malaria district deserves more consideration than the mere statement that they become "accustomed to" malarial infection; will not, I ask, serological investigations reveal the nature of the changes that have rendered the blood resistant—and so give us assistance in treatment?

Take the case of blackwater fever: here you have great populations practically absolutely immune. That immunity is not racial—is it inherited or is it acquired in infancy? It has long seemed to me that serological investigations amongst these immune people will probably throw much light on the real nature of blackwater fever and guide us in dealing with it. The history of many of these cases, *i.e.*, a series of small febrile attacks, hardly incapacitating, at short intervals ending in the sudden explosion is suggestive of something of the nature of anaphylaxis.

We have now, with our Allies, a very large stake in the Eastern Mediterranean—especially at Salonica; it is vitally necessary to preserve the effectiveness of that force by every means in our power. I do not know whether any investigations have been made into the prevalence of

malarial fevers, and also the powers of resistance to them, amongst the inhabitants in the districts occupied by our troops; a considerable number of cases of blackwater fever have occurred in the army there—to what extent does it prevail amongst the inhabitants? and would not serological investigations yield information which might be turned to great practical account?

Sir WILLIAM OSLER threw out a suggestive remark that as with the *Spirochæta pallida* so with malaria, once infected, infected for life—need that be so?

The greatest advances in the treatment of syphilis have been made not so much by the possession of new means of treatment of the salvarsan type as by the development of the means of detection of activity of the disease by examination of the blood serum, and still more, by that of the cerebro-spinal fluid.

I wish to add just one word on the subject of prophylaxis by quinine; that is a question which I have long thought cannot be satisfactorily settled until systematic observations have been carried out with regard to the absorption of quinine, its period of retention and rate of excretion, and for that reason I have heard with pleasure of the experiments of Staff-Sergeant NIERENSTEIN, from which information of practical use in this question may, I hope, be obtained.

The CHAIRMAN: As I have never worked specially at malaria, I shall not add to the discussion. Major ELLIOT'S warning in regard to the effect of large doses of quinine reminds me of an incident in my youth, when I was a young medical officer in Malta. There we had a shrewd old Scotsman, Surgeon-General JAMES SINCLAIR, as Principal Medical Officer. Before I had been on the island many months I had a difference of opinion with the Senior Medical Officer of the hospital on the subject of the giving of medicine. My idea was to give as little as possible, and only if some good effect might be reasonably expected. He reported me for this offence and in due time we appeared before the Principal Medical Officer. The Senior Medical Officer made his complaint. The Principal Medical Officer said, in reply, as he sat at his desk looking straight in front of him, "I always like a patient to die of his disease!"